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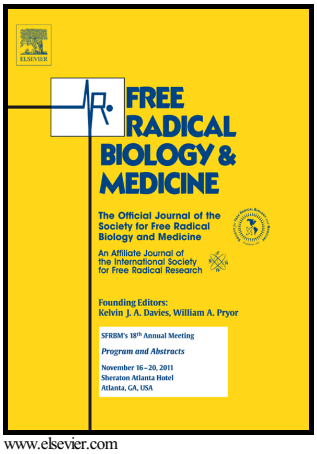

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Clinical aspects and biomarkers of Alzheimer's disease in Down syndrome

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Abstract (187 words)

Alzheimer's disease (AD) may affect in excess of 90% of individuals with Down syndrome (DS) after age 60, due to duplication of the APP gene in trisomy of chromosome 21, with neuropathology that is comparable to Sporadic AD and Familial AD (FAD). Previous literature suggested some unique features in clinical presentation of dementia in DS (DSd), which might be due to diagnostic difficulties, or represent a real difference compared to SAD or FAD. We review current knowledge on clinical diagnosis and presentation of dementia in DS in comparison with FAD due to APP mutations and APP duplication. We suggest that the clinical presentation in DS (prominent memory decline and behavioral symptoms, and early development of myoclonus and seizures) are similar to the clinical features associated with APP mutations that is known to have an increased Aβ42/ Aβ40 ratio, and highlight the relative lack of vascular complications associated with cerebral amyloid angiopathy in DS in comparison with those rare individuals with FAD due to duplication APP. We consider the biomarker evidence associated with DS and DSd with reference to Aβ peptide levels and oxidative stress, and suggest future directions for research to explore the potential mechanisms associated with the clinical presentation of DSd.

1. Introduction

Almost all older adults with Down syndrome (DS) have the neuropathological hallmarks of Alzheimer's disease (AD) at post-mortem, consisting of progressive build-up of extracellular amyloid- (Aβ) plaques and intraneuronal hyperphosphorylated tau [1], which can now also be demonstrated with in-vivo amyloid PET imaging techniques [2, 3]. As all individuals with DS over the age of 50 who have undergone amyloid PET imaging have been shown to have significant amyloid deposition, AD brain pathology is probably universal in ageing individuals with DS.

At the gross pathological level, AD in DS is similar to the AD pathology associated with sporadic Alzheimer's disease (SAD), and many types of familial Alzheimer's disease (FAD). However, there are important differences in terms of genetic mechanisms between DS, SAD, and FAD. In DS with trisomy of human chromosome 21, AD is believed to be related to triplication of the APP gene, and the basic mechanism leading to the AD pathology is lifelong overproduction of APP, which is associated with deposition of Aβ [4]. DS is therefore comparable to Aβ overproduction associated with several other FAD mutations, while reduced clearance of Aβ is implicated in SAD [5].

In this review, we will summarize the clinical presentation of AD in DS before considering current knowledge on fluid biomarkers associated with AD in DS in order to highlight similarities and differences with other types of AD, particularly FAD due to APP duplication and other APP mutations.

2. Epidemiology of AD in DS

In keeping with the pathological data, dementia is exceptionally common in older adults with Down syndrome, though as with SAD and FAD with a time lag of several decades after the development of AD pathology. Clinical dementia diagnoses show a sharp age-related increase in prevalence (i.e. cross-sectional rates), from less than 10% by age 49 to more than 30% by age 60 [6]. However, as dementia is now a common cause of death in people with Down syndrome [7], prevalence rates may underestimate overall risk and longitudinal studies show that the cumulative incidence for dementia in people with Down syndrome is in excess of 90% by age 65 [8]. Although prevalence rates may go down with age (particularly after age 60) due to increased mortality in older individuals with DS and dementia (DSd) [9], incidence (rate of new cases) increased steadily with increasing age and did not decline after age 60, from 2.5 per 100 person years in those aged <50 to 13.31 per 100 person years in those aged 60 and older [9].

While age is a strong common risk factor, DSd is thus similar to FAD with a much earlier age of onset, several decades before the typical onset seen in SAD. In families with PSEN1 mutations, for example, the typically age at diagnosis is within the range 35-55 years, but cognitive symptoms may manifest earlier, while those with PSEN2 mutations present between 40-70 years [10]. Individuals with APP mutations tend to have symptom onset between 40-65 years. DSd is thus comparable to FAD in terms of age of onset of dementia.

No gender differences have been found for dementia rates in older adults with DS [9, 11], but the average age of menopause of women with DS was younger than in the general population, and the age at onset of dementia was correlated with the age of menopause for those who developed dementia [12].

3. Clinical diagnosis of AD in DS

Dementia is clinically defined as a progressive brain disorder which particularly affects higher cortical functions such as memory, language and orientation, and which eventually leads to death [13]. There are challenges to diagnosing dementia in individuals with DS. These include premorbid intellectual impairment and functional difficulties that need to be distinguished from subsequent

decline, varying baseline functioning, and limitations in speech abilities, which means the usual AD screening and diagnostic tools may not be suitable in DS [6, 14]. The development of dementia symptoms also need to be understood in the context of a typical DS cognitive phenotype, including impairments in executive function, memory and motor coordination [15]. Therefore, a diagnostic work-up needs to carefully establish the presence of cognitive deterioration that is typical of AD in DS, with reference to the person's own baseline, while excluding common co-morbidities such as depression or thyroid dysfunction which are also common causes of apparent decline in DS [16]. Several diagnostic systems are available to diagnose dementia. The International Statistical Classification of Diseases (ICD) 10 system's criteria include decline in memory, together with decline in other cognitive abilities such as organization, judgement and information processing and decline of emotional control and social behavior such as emotional lability and apathy [13]. The Diagnostic and Statistical Manual (DSM) system has a similar definition, though does not require the presence of behavioral change in the form of decline in emotional control and social behavior. The DSM-IV was found to be more inclusive than ICD-10 when used in individuals with intellectual disability [17], but predictive validity was less good when used in individuals with more severe intellectual disability and sensory deficits than in the general population despite good inter-rater reliability [18]. Overall a clinical diagnosis of dementia appeared to be more reliable in individuals with DS than these standard criteria and enabled clinicians to diagnose more cases of individuals with DS with AD [18], suggesting that there are some issues when applying standard criteria in the presence of premorbid cognitive impairment. There are however newer versions of criteria, such as the DSM-5 neurocognitive disorder diagnosis, which may help to improve accuracy of diagnosis in DS [19]. Interestingly, the DSM5 and other newer research criteria view DS as a genetic cause of AD, which potentially allows for a diagnosis of probable AD even if symptoms are relatively mild.

4. Presenting symptoms in DS compared to FAD and SAD

Memory decline is viewed as the key symptom associated with AD, and the majority of individuals with SAD and FAD present with early impairment of episodic memory, which gradually progresses to involve other cognitive domains. However, there are possibly some subtle differences between SAD and FAD. Longitudinal studies of FAD mutation carriers showed that the earliest neuropsychological changes were a decline in verbal memory, which occurred approximately 3 years before symptoms became apparent [20]. Similarly, SAD is also preceded by a relatively long

prodromal stage, with an amnestic picture, such as that described in mild cognitive impairment [21]. Nevertheless, atypical presentations are often reported in FAD and also exist in SAD. Behavioral and psychiatric symptoms of dementia (BPSD) such as agitation, depression, delusions and hallucinations occur commonly in SAD as the disease progresses. Early BPSD may also occasionally be a feature of PSEN1 and PSEN2 mutations which become more prominent during the course of the disease [10].

4.1 Typical DS dementia presentation

There is ongoing debate whether there are significant differences in dementia presentation in DS compared to SAD or FAD. Previous studies suggested that BPSD's may precede memory impairment [22] in keeping with a frontal-like syndrome [23]. Several studies have described BPSD's that often precede dementia diagnosis in adults with DS [24 – 26]. Individuals with DSd often present with behavioral problems [27, 28], which can be divided into two types – behavioral excesses such as irritability, aggression or self-abusive behavior, or behavioral deficits such as general slowness, apathy or loss of interest and decreased social engagement; behavioral excesses rather than deficits may trigger referral for dementia assessment [29], suggesting that caregivers' bias may influence reporting and referral for symptoms. Caregivers reported forgetfulness and confusion as well as 'frontal lobe'-related symptoms such as slowness in activities and speech, loss of interest and withdrawal, along with the emergence of emotional and behavior problems as common presenting symptoms of dementia [30]. More recently, Dick et al. compared the neuropsychological profiles of higher-functioning DS individuals with dementia to individuals with advanced SAD while adjusting for gender and levels of functional impairment [31]. They found similarities in presentation, suggesting the underlying pathology may have comparable effects on cognitive profiles in both DS and SAD, at least during the later stages of AD.

Establishing the sequence of early cognitive changes in DS associated with progression during prodromal AD remains a challenge. However, using longitudinal studies, it has been shown that changes in short-term recall and explicit memory may occur several years before a dementia diagnosis [32, 33] and recently it has been reported that immediate memory impairment may be one of the earliest signs of dementia in people with DS [34]. It is not clear what proportion of DS individuals initially present with the typical changes in memory domains that is typical of SAD, or with the atypical presentations associated with some of the FAD mutation carriers. In addition, language-based tasks are inherently difficult for individuals with DS, given the typical DS premorbid cognitive profile (which includes short-term verbal memory deficits) [35]. A better

understanding of the sequence of decline in the presymptomatic and early stages of DSd is required to identify suitable outcome measures for future clinical trials.

4.2 Unusual clinical presentations

Visuospatial and visuoperceptual deficits commonly occur in the later stages of both SAD and FAD. The posterior cortical atrophy (PCA) variant of SAD is now well-recognized, with prominent visual processing deficits while memory is relatively preserved until later in the disease [36]. PCA may resent with earlier onset and affects parietal, occipital and occipito-temporal brain regions, therefore have an impact on literacy, numeracy and praxis. Some studies have found increased neurofibrillary tangles but similar amyloid plaque density in visual areas, with fewer tangles or plaques in the hippocampus in PCA compared to typical SAD, possibly associated with particular genetic status (including APOE4) [37]. There are no data on PCA-like presentations in DS, but anecdotally some individuals may present with visuoperceptual difficulties including difficulty managing stairs or steps, being scared of sitting on chairs and having difficulty managing toiletting due to not being able to discriminate toilet seats from background colors [38].

4.3 Neurological symptoms and signs

Neurological symptoms and signs tend to be more prominent in FAD than SAD, and is also common in DSd. Up to half of DS dementia cases may present with neurological symptoms, such as seizures and incontinence, which are normally signs associated with advanced disease in SAD, suggesting that dementia presents atypically in DS, or reflecting the diagnostic difficulties, particularly in those with more severe ID [6]. In FAD, seizures seem to be reported more frequently and at an earlier stage in the disease than in SAD, occurring in more than a third with APP mutations [10]. Early myoclonus and seizures are observed in individuals with *APP* mutations and particularly those with *APP* duplications (table 1).

Myoclonus and seizures are also very common in DS dementia, and have been described as the presenting symptom in some cases of especially in those with severe ID [11, 39 – 41]. Seizures are also predictive of rate of decline [42]. Indeed, seizures are so strongly associated with AD in older individuals with DS that the onset of seizures in older age should trigger an assessment for dementia [38]. Seizures are commonly myoclonic or tonic-clonic types, with an earlier picture characterized by myoclonic jerks on awakening, and progression to generalized tonic-clonic seizures. EEG may reveal generalized slowing or spike and wave pattern [43, 44].

Parkinsonism and cerebellar signs do not usually become apparent until several years into the clinical course of SAD, but may be more strongly associated with some forms as FAD, such as PSEN1 and PSEN2 mutations. Cerebellar Aβ deposition is a common feature in both FAD and SAD. Extrapyramidal signs such as rigidity, bradykinesia and an abnormal posture and gait has also been described in DS dementia [40] and by end-stage, all individuals were unable to walk and incontinent, and almost all had seizures [8] and many had Parkinsonian features [39, 41]. Cerebellar ataxia may however be an overlooked sign of dementia in DS, since brains of elderly patients with Down syndrome have also been found to have significant cerebellar Aβ deposition [45].

5. APP mutations and APP duplications compared to DS

The APP gene is situated on chromosome 21, and mutations in this gene is therefore of particular interest in comparison with DS. The majority of pathogenic APP mutations affect the β and γ secretase cleavage sites of the protein, while in the case of APP duplications, there is an extra copy of the whole of the APP region on chromosome 21. These individuals with APP microduplications therefore have the same genetic mechanism for AD as in DS, while not having extra copies of most of the other genes on the rest of chromosome 21 and therefore do not present with features of DS such as intellectual impairment or congenital heart conditions [4].

APP mutations can be classified according to their biological effect on Aβ levels (table 1). Firstly, mutations that increase total Aβ without changing the Aβ42/40 ratio, such as the Swedish mutation at APP670/671, are associated in affected individuals with prominent memory loss and a classic Alzheimer's disease presentation [46].

Other APP mutations result in increased Aβ42 levels, altering the AB42/40 ratio. Of this type, the 'London' *APP* V717I mutation has a change at the 717 codon close to the γ secretase site. Families with this mutation were found to present with early impairment of episodic memory, lack of insight and prominent myoclonus and seizures [47]. A so-called Austrian mutation (T714I) results in a 11x increase in Aβ42 levels, and presented clinically with rapidly progressive and very early onset dementia with early memory loss, seizures, myoclonus, parkinsonism, spasticity, and behavioral symptoms. It was at post-mortem found to be associated with notably absent Aβ40 from amyloid deposits in the brain, and the deposits were largely in the form of "cloudy" diffuse plaques with a non-neuritic cotton-wool appearance [48].

Some APP mutations result in changes in Aβ aggregation. These include the 'Dutch mutation' (E693Q) with a distinct phenotype with severe cerebral amyloid angiopathy (CAA) leading to recurrent cerebral hemorrhage (ICH) and consequent focal neurological symptoms and signs. Most patients also develop dementia [49]. A neighboring mutation at position 692 (Flemish mutation) has also been reported to present with hemorrhages and a progressive dementia associated with CAA [50]. Interestingly, this mutation has been shown to inhibit aggregation, but fibril formation is specifically increased through interaction with gangliosides in the vascular wall, resulting in CAA [51]. The Iowa mutation (D694N) also promotes fibrillogenesis of Aβ with severe CAA on pathological investigation, widespread neurofibrillary tangles and amyloid plaques with particularly prominent Aβ40 deposition often resulting in ICH and hemorrhagic stroke [52].

Duplications of the *APP* gene can also cause FAD with a cognitive phenotype that is similar to SAD, with early progressive impairment of episodic memory but with an onset age of between 39 and 64 years [53-55]. Characteristic features include seizures (up to 57%) as well as prominent amyloid angiopathy (CAA) with hemorrhagic stroke occurring in a third of individuals [56]. In comparison, ICH and stroke appears to be rarer (3-4%) in individuals with DSd [57] despite the similar APP mechanism.

At the clinical level, DSd therefore seems to present with a symptoms similar to those APP mutations that have an altered Aβ42/40 ratio, and unlike FAD due to APP duplication, seems to be somewhat protected against ICH and hemorrhagic stroke, suggesting the potential presence of a mechanism/s associated with chromosome 21 triplication that shifts the risk away from vascular complications. Such a protective mechanism might involve amyloid processing or clearance, vascular protective factors, a unique oxidative stress profile or immune response [56]. We next review biomarker evidence, with a particular focus on biomarkers that might shed light on the apparent difference in clinical presentation of dementia between duplication APP and trisomy 21.

6. Fluid biomarkers of AD in DS (table 2)

Biomarkers are objective measures of a biological or pathogenic process that can be used to estimate the risk for developing a disease, to guide clinical diagnosis, to evaluate prognosis, to monitor progression and/or response to therapeutic interventions [58]. Biomarkers can be found in different types of fluids, including blood (serum or plasma), cerebrovascular fluid (CSF), and urine.

6.1. Peripheral fluid biomarkers

6.1.1. Blood biomarkers

The advantage of plasma and serum is that they are easily available and considered as relatively non-invasive. In AD several novel blood biomarkers have been proposed, although verification and validation in independent studies remains to be further established [59].

Amyloid-beta

Amyloid-beta plays a central role in the pathogenesis of Alzheimer's disease (AD) and has been postulated as a potential biomarker for AD in the general population [60]. DS subjects show higher plasma Aβ42 and Aβ40 levels compared to cognitively normal subjects without trisomy 21 [61, 62]. Although some studies found no differences comparing DS with and without dementia, an association between Aβ levels and neuropsychological scores in multivariable adjusted models was found [61, 63]. Also, demented DS subjects with longer dementia duration showed higher Aβ42, lower Aβ40 and a higher Aβ42/Aβ40 ratio than those with shorter dementia duration [63]. Two other studies comparing DSd to cognitively normal DS found a higher Aβ42/Aβ40 ratio in DSd [64] and increased Aβ40 levels in DSd subjects [65], having adjusted for age and gender, that remained stable during a follow-up of several years. It is however difficult to draw any conclusions from these studies with regard to Aβ42/Aβ40 ratios in DS given the relatively weak correlation between these peripheral measurements and central Aβ.

Tau

Tau are proteins that stabilize microtubules and they are abundant in neurons of the central nervous system [66]. Plasma tau levels are elevated in AD but with overlapping ranges across diagnostic groups [67], which diminishes the utility of plasma tau as a diagnostic test [67, 68]. DS subjects, with or without dementia, also show higher plasma tau levels compared to age-matched normal subjects [69]. As tau levels correlate with cognitive scores, plasma tau levels in DS may indicate early neurodegeneration [69].

Oxidative stress markers

Although AD is probably associated with multiple etiologies and pathophysiologic mechanisms, oxidative stress appears as a major part of the pathophysiologic process [70]. The anti-oxidant system is affected in DS, even before the onset of AD, and implicated in the cognitive phenotype associated with the chromosomal disorder; however the variations in the phenotype might result

from several possible gene or gene product interactions [71]. Studies in young people with DS revealed a systemic and exacerbated oxidative stress [72], which increases with age [73].

In DS subjects, low superoxide dismutase/glutathione peroxidase (SOD1/GPx) ratios are associated with worse memory ability [74] and in a longitudinal study it was shown that superoxide dismutase enzyme levels are associated with memory decline over time [75].

Neopterin, an unconjugated pteridine that is secreted in large quantities by activated macrophages, can be used as a clinical marker of activated cellular immunity and oxidative stress in AD [76]. Plasma neopterin levels have been found to be higher in patients with AD in general [77, 78] and people with DS and AD in particular [79, 80].

In summary, DS is associated with increased oxidative stress, which is present even in younger individuals, and it appears that markers of oxidative stress worsen during ageing, and with the development of AD in DS. Higher superoxide dismutase levels relative to glutathione peroxidase could protect against decline but it is not clear how this and other effects related to trisomy 21 affect the presentation of dementia in DS, or whether it could explain apparent differences with individuals with FAD due to APP microduplication.

6.1.2 Urine biomarkers

Similarly to blood, the advantage of urine is that it is easily obtainable and non-invasive. Although few urine biomarkers have been studied in the general AD population (such as neural thread protein, a phosphoprotein associated with the neurofibrillary tangles of AD [81, 82], no specific studies of urine biomarker of AD in DS have been conducted to date other than urine markers of oxidative stress or activated cellular immunity.

Isoprostane 8,12-iso-iPF2alpha

Isoprostane 8,12-iso-iPF2alpha are chemically stable, sensitive and specific biomarkers of lipid peroxidation in vivo [83] and have been shown to be increased in Alzheimer's disease [84], and may mediate the neuronal response to oxidative stress [85]. In a longitudinal study in subjects with DS, it was shown that change in iPF2alpha levels over time may have potential as a biomarker for memory decline in DS and potentially also help to track progression of MCI to AD [86].

Neopterin

Similarly to the findings in plasma neopterin levels described above, urine neopterin might also have a potential as a biomarker of AD in DS. In a longitudinal study involving individuals with DS it was shown that neopterin/creatinine levels correlated with cognitive performance over time [87].

6.2. CSF biomarkers

A major advantage of CSF biomarkers is the fact that proteins or peptides that may be directly reflective of brain specific activities as well as disease pathology would most likely diffuse into CSF rather than into any other bodily fluid [88]. However, CSF is not easily available and collection is invasive through lumbar puncture. As a result, few CSF studies in DS have been conducted, with very small numbers of participants [89]. However, in a recent systematic review and meta-analysis of biomarkers for the diagnosis of Alzheimer's disease in the general population it was clearly shown that the core CSF biomarkers of neurodegeneration (amyloid-beta, P-tau and and T-tau) are strongly associated with AD mild cognitive impairment and due to their consistency CSF biomarkers should be used in clinical practice and clinical research [90]. In particular, in AD patients, T-tau is on average 2.5 times higher in CSF compared to controls, P-tau is almost 2 times higher in CSF compared to controls, when Aβ42 is almost 2 times lower in CSF compared to controls [90].

Amyloid-beta

CSF Aβ42 levels are lower in DS compared to non-DS control subjects and correlate negatively with age in the DS population [91]. In early childhood, Aβ levels tend to increase in DS, followed by a gradual decrease (reduced clearance from the brain) once the deposition of Aβ42 into plaques augments, similar to the pattern also observed in SAD and FAD [92]. Well-designed longitudinal data from larger studies to track change over time, and to compare CSF amyloid-beta levels between demented DS patients and non-demented DS, and to make comparisons with individuals with APP mutations or duplication APP are not yet available.

Tau

CSF tau levels do not differ between DS and control subjects but appear to correlate positively with age in DS individuals [91]. Well-designed large studies comparing CSF tau levels between demented DS patients and non-demented DS are not yet available, and it is thus unknown how changes in CSF tau levels relate to the development of dementia, or whether it might help to distinguish DS individuals with and without AD.

Presenilin-1

Presenelin-1 is one of the core proteins in the gamma sectretase complex, involved in APP processing. CSF presenilin-1 shows an age-dependent increase in cognitively normal controls [93]. However, the total levels of CSF presenilin-1 increased in subjects with autosomal dominant AD that carried PSEN1 mutations but also in DS individuals (ten demented and ten non-demented DS), compared with age-matched controls, even prior to the appearance of symptoms of dementia [93]. The implications of this finding are not clear, but CSF presenilin-1 appears to have potential as an early biomarker for AD in DS.

Oxidative stress markers

Studies involving oxidative stress markers in CSF have only been conducted in small studies of non-DS patients with MCI. Such patients present with higher isoprostane 8, 12-iso-iPF2alpha (iPF2alpha) levels in CSF compared to cognitively normal elderly subjects [94]. This finding suggests that increased brain oxidative damage precedes the onset of symptomatic dementia and that measurement of this isoprostane may identify a subgroup of patients with MCI with increased lipid peroxidation who are at increased risk to progress to symptomatic AD [94]. A well-designed large study comparing CSF iPF2alpha levels between demented DS patients and non-demented DS is not yet available.

7. Conclusions and future directions

The 40-amino-acid peptide Aβ (Aβ 40) is more soluble than the longer Aβ 42 peptide and tends to be the major form of Aβ in the artery walls in CAA, while Aβ 42 is more prominent in plaques. In mutations where Aβ 42 is increased, such as the Indiana and London APP mutations, vascular amyloid seems to be a less prominent feature than parenchymal plaques. In contrast, if a low Aβ 42/40 ratio is present, and in those mutations that result in altered fibril formation, CAA is promoted. The clinical presentation of AD in DS, with cognitive decline and worsening memory impairment in combination with behavioral changes, myoclonus and seizures, are comparable to APP mutations that result in increased Aβ42 levels relative to Aβ40 (and possibly other smaller Aβ peptides). Furthermore, in DS there is some evidence for a degree of protection against the CAA and ICH phenotypes usually associated with APP duplication, although a moderate degree of CAA and microbleeds have been demonstrated in DS neuropathological studies.

Though peripheral fluid biomarkers are more accessible, CSF biomarkers, similarly to their role in AD in the general population, probably have better potential in predicting AD or monitoring

cognitive function in DS, and also need to be used to make comparisons with FAD, particularly the different forms of APP mutations and APP duplication. More studies including CSF biomarkers are needed in DS.

The underlying mechanism for the typical presentation of DSd is not clear. However, Amyloid Protein Precursor (APP) is processed in the endo-lysosomal compartment, and modifications within these pathways may therefore contribute to changes in Aβ concentrations involved in the onset of AD. The endo-lysosomal compartment is morphologically different in DS peripheral cells compared to euploid cells [95], and enlarged endosomes have been described in neuronal cells from post-mortem brains of individuals with SAD and DS [96]. The implications of these differences in terms of amyloid processing and Aβ peptides need to be further explored, as well as to identify the underlying mechanisms.

Finally, markers of oxidative stress have potential as biomarkers of cognitive function in DS populations. However, more longitudinal and case-controlled studies are needed to confirm the exact role of oxidative stress in pathogenesis of AD in DS, as well as its role in the clinical presentation of dementia in DS.

References

1. Mann DM. Alzheimer's disease and Down's syndrome. Histopathology. 1988 Aug;13(2):125-37.

2. Landt J, D'Abrera JC, Holland AJ, Aigbirhio FI, Fryer TD, Canales R, Hong YT, Menon DK, Baron JC, Zaman SH. Using positron emission tomography and Carbon 11-labeled Pittsburgh Compound B to image Brain Fibrillar β-amyloid in adults with down syndrome: safety, acceptability, and feasibility. Arch Neurol. 2011 Jul;68(7):890-6.

3. Hartley SL, Handen BL, Devenny DA, Hardison R, Mihaila I, Price JC, Cohen AD, Klunk WE, Mailick MR, Johnson SC, Christian BT. Cognitive functioning in relation to brain amyloid-β in healthy adults with Down syndrome. Brain. 2014 Sep;137(Pt 9):2556-63.

4. Wiseman FK, Al-Janabi T, Hardy J, Karmiloff-Smith A, Nizetic D, Tybulewicz VL, Fisher EM, Strydom A. A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. Nat Rev Neurosci. 2015 Sep;16(9):564-74.

5. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med. 2016 Jun 1;8(6):595-608.

6. Strydom A, Shooshtari S, Lee L, Raykar V, Torr J, Tsiouris J, Jokinen N, Courtenay K, Bass N, Sinnema M, Maaskant M. Dementia in older adults with intellectual disabilities—epidemiology, presentation, and diagnosis. Journal of Policy and Practice in Intellectual Disabilities. 2010 Jun 1;7(2):96-110.

7. Englund A, Jonsson B, Zander CS, Gustafsson J, Annerén G. Changes in mortality and causes of death in the Swedish Down syndrome population. Am J Med Genet A. 2013 Apr;161A(4):642-9.

8. McCarron M, McCallion P, Reilly E, Mulryan N. A prospective 14-year longitudinal follow-up of dementia in persons with Down syndrome. J Intellect Disabil Res. 2014 Jan;58(1):61-70.

9. Coppus A, Evenhuis H, Verberne GJ, Visser F, van Gool P, Eikelenboom P, van Duijin C. Dementia and mortality in persons with Down's syndrome. J Intellect Disabil Res. 2006 Oct;50(Pt 10):768-77.

10. Ryan NS, Nicholas JM, Weston PS, Liang Y, Lashley T, Guerreiro R, Adamson G, Kenny J, Beck J, Chavez-Gutierrez L, de Strooper B, Revesz T, Holton J, Mead S, Rossor MN, Fox NC. Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series. Lancet Neurol. 2016 Dec;15(13):1326-1335.

11. Tyrrell J, Cosgrave M, McCarron M, McPherson J, Calvert J, Kelly A, McLaughlin M, Gill M, Lawlor BA. Dementia in people with Down's syndrome. Int J Geriatr Psychiatry. 2001 Dec;16(12):1168-74.

12. Coppus AM, Evenhuis HM, Verberne GJ, Visser FE, Eikelenboom P, van Gool WA, Janssens AC, van Duijn CM. Early age at menopause is associated with increased risk of dementia and mortality in women with Down syndrome. J Alzheimers Dis. 2010;19(2):545-50.

13. World Health Organization. ICD-10, the ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research. Geneva: World Health Organization. 1993.

14. Strydom A, Hassiotis A, King M, Livingston G. The relationship of dementia prevalence in older adults with intellectual disability (ID) to age and severity of ID. Psychological Medicine. 2009 Jan;39(1):13-21.

15. Startin CM, Hamburg S, Hithersay R, Davies A, Rodger E, Aggarwal N, Al-Janabi T, Strydom A. The LonDownS adult cognitive assessment to study cognitive abilities and decline in Down syndrome. Wellcome Open Res. 2016 Nov 15;1:11.

16. Strydom A, Al-Janabi T, Houston M, Ridley J. Best practice in caring for adults with dementia and learning disabilities. Nurs Stand. 2016 Oct 5;31(6):42-51.

17. Strydom A., Livingston G., King M., Hassiotis A. Prevalence of dementia in intellectual disability using different diagnostic criteria. Br J Psychiatry. 2007;191:150–157

18. Sheehan R, Sinai A, Bass N, Blatchford P, Bohnen I, Bonell S, Courtenay K, Hassiotis A, Markar T, McCarthy J, Mukherji K, Naeem A, Paschos D, Perez-Achiaga N, Sharma V, Thomas D, Walker Z, Strydom A. Dementia diagnostic criteria in Down syndrome. Int J Geriatr Psychiatry. 2015 Aug;30(8):857-63

19. Fletcher RJ, Barnhill J, McCarthy J, Strydom A. From DSM to DM-ID. Journal of Mental Health Research in Intellectual Disabilities. 2016 Jul 2;9(3):189-204.

20. Fox NC, Kennedy AM, Harvey RJ, Lantos PL, Roques PK, Collinge J, Hardy J, Hutton M, Stevens JM, Warrington EK, Rossor MN. Clinicopathological features of familial Alzheimer's disease associated with the M139V mutation in the presenilin 1 gene. Pedigree but not mutation specific age at onset provides evidence for a further genetic factor. Brain. 1997 Mar;120 (Pt 3):491-501.

21. Geda YE. Mild cognitive impairment in older adults. Curr Psychiatry Rep. 2012 Aug;14(4):320-7.

22. Dekker AD, Strydom A, Coppus AM, Nizetic D, Vermeiren Y, Naudé PJ, Van Dam D, Potier MC, Fortea J, De Deyn PP. Behavioural and psychological symptoms of dementia in Down syndrome: Early indicators of clinical Alzheimer's disease? Cortex. 2015 Dec;73:36-61.

23. Ball SL, Holland AJ, Treppner P, Watson PC, Huppert FA. Executive dysfunction and its association with personality and behaviour changes in the development of Alzheimer's disease in adults with

Down syndrome and mild to moderate learning disabilities. Br J Clin Psychol. 2008 Mar;47(Pt 1):1-29.

24. Ball SL, Holland AJ, Hon J, Huppert FA, Treppner P, Watson PC. Personality and behaviour changes mark the early stages of Alzheimer's disease in adults with Down's syndrome: findings from a prospective population-based study. Int J Geriatr Psychiatry. 2006 Jul;21(7):661-73.

25. Holland AJ, Hon J, Huppert FA, Stevens F. Incidence and course of dementia in people with Down's syndrome: findings from a population-based study. J Intellect Disabil Res. 2000 Apr;44 (Pt 2):138-46.

26. Nelson LD, Orme D, Osann K, Lott IT. Neurological changes and emotional functioning in adults with Down Syndrome. J Intellect Disabil Res. 2001 Oct;45(Pt 5):450-6.

27. Prasher VP, Chung MC, Haque MS. Longitudinal changes in adaptive behavior in adults with Down syndrome: interim findings from a longitudinal study. Am J Ment Retard. 1998 Jul;103(1):40-6.

28. Urv TK, Zigman WB, Silverman W. Maladaptive behaviors related to dementia status in adults with Down syndrome. Am J Ment Retard. 2008 Mar;113(2):73-86

29. Oliver C, Kalsy S, McQuillan S, Hall S. Behavioural excesses and deficits associated with dementia in adults who have Down syndrome. Journal of Applied Research in Intellectual Disabilities. 2011 May 1;24(3):208-16.

30. Deb S, Hare M, Prior L. Symptoms of dementia among adults with Down's syndrome: a qualitative study. J Intellect Disabil Res. 2007 Sep;51(Pt 9):726-39.

31. Dick MB, Doran E, Phelan M, Lott IT. Cognitive Profiles on the Severe Impairment Battery Are Similar in Alzheimer Disease and Down Syndrome With Dementia. Alzheimer Dis Assoc Disord. 2016 Jul-Sep;30(3):251-7

32. Devenny DA, Krinsky-McHale SJ, Sersen G, Silverman WP. Sequence of cognitive decline in dementia in adults with Down's syndrome. J Intellect Disabil Res. 2000 Dec;44 (Pt 6):654-65.

33. Krinsky-McHale SJ, Devenny DA, Silverman WP. Changes in explicit memory associated with early dementia in adults with Down's syndrome. J Intellect Disabil Res. 2002 Mar;46(Pt 3):198-208.

34. Blok JB, Scheirs JG, Thijm NS. Personality and behavioural changes do not precede memory problems as possible signs of dementia in ageing people with Down syndrome. Int J Geriatr Psychiatry. 2016 Oct 4. doi: 10.1002/gps.4606.

35. Vicari S, Pontillo M, Armando M. Neurodevelopmental and psychiatric issues in Down's syndrome: assessment and intervention. Psychiatr Genet. 2013 Jun;23(3):95-107

36. Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. Lancet Neurol. 2012 Feb;11(2):170-8.

37. Schott JM, Crutch SJ, Carrasquillo MM, Uphill J, Shakespeare TJ, Ryan NS, Yong KX, Lehmann M, Ertekin-Taner N, Graff-Radford NR, Boeve BF, Murray ME, Khan QU, Petersen RC, Dickson DW, Knopman DS, Rabinovici GD, Miller BL, González AS, Gil-Néciga E, Snowden JS, Harris J, Pickering-Brown SM, Louwersheimer E, van der Flier WM, Scheltens P, Pijnenburg YA, Galasko D, Sarazin M, Dubois B, Magnin E, Galimberti D, Scarpini E, Cappa SF, Hodges JR, Halliday GM, Bartley L, Carrillo MC, Bras JT, Hardy J, Rossor MN, Collinge J, Fox NC, Mead S. Genetic risk factors for the posterior cortical atrophy variant of Alzheimer's disease. Alzheimers Dement. 2016 Aug;12(8):862-71.

38. British Psychological Society. Dementia and People with Intellectual Disabilities - Guidance on the assessment, diagnosis, interventions and support of people with intellectual disabilities who develop dementia.Leicester. 2015

39. Cosgrave MP, Tyrrell J, McCarron M, Gill M, Lawlor BA. A five year follow-up study of dementia in persons with Down's syndrome: Early symptoms and patterns of deterioration. Irish Journal of Psychological Medicine. 2000 Mar;17(1):5-11.

40. Margallo-Lana ML, Moore PB, Kay DW, Perry RH, Reid BE, Berney TP, Tyrer SP. Fifteen-year follow-up of 92 hospitalized adults with Down's syndrome: incidence of cognitive decline, its relationship to age and neuropathology. J Intellect Disabil Res. 2007 Jun;51(Pt. 6):463-77.

41. Visser FE, Aldenkamp AP, van Huffelen AC, Kuilman M, Overweg J, van Wijk J. Prospective study of the prevalence of Alzheimer-type dementia in institutionalized individuals with Down syndrome. Am J Ment Retard. 1997 Jan;101(4):400-12.

42. Lott IT, Doran E, Nguyen VQ, Tournay A, Movsesyan N, Gillen DL. Down syndrome and dementia: seizures and cognitive decline. J Alzheimers Dis. 2012;29(1):177-85.

43. Aller-Alvarez JS, Menéndez-González M, Ribacoba-Montero R, Salvado M, Vega V, Suárez-Moro R, Sueiras M, Toledo M, Salas-Puig J, Álvarez-Sabin J. Myoclonic epilepsy in Down syndrome and Alzheimer disease. Neurologia. 2017 Mar;32(2):69-73.

44. De Simone R, Puig XS, Gélisse P, Crespel A, Genton P. Senile myoclonic epilepsy: delineation of a common condition associated with Alzheimer's disease in Down syndrome. Seizure. 2010 Sep;19(7):383-9

45. Mann DM, Iwatsubo T. Diffuse plaques in the cerebellum and corpus striatum in Down's syndrome contain amyloid beta protein (A beta) only in the form of A beta 42(43). Neurodegeneration. 1996 Jun;5(2):115-20.

46. Mullan M, Crawford F, Axelman K, Houlden H, Lilius L, Winblad B, Lannfelt L. A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid. Nat Genet. 1992 Aug;1(5):345-7

47. Rossor MN, Newman S, Frackowiak RS, Lantos P, Kennedy AM. Alzheimer's disease families with amyloid precursor protein mutations. Ann N Y Acad Sci. 1993 Sep 24;695:198-202

48. Kumar-Singh S, De Jonghe C, Cruts M, Kleinert R, Wang R, Mercken M, De Strooper B, Vanderstichele H, Löfgren A, Vanderhoeven I, Backhovens H, Vanmechelen E, Kroisel PM, Van Broeckhoven C. Nonfibrillar diffuse amyloid deposition due to a gamma(42)-secretase site mutation points to an essential role for N-truncated A beta(42) in Alzheimer's disease. Hum Mol Genet. 2000 Nov 1;9(18):2589-98.

49. Van Broeckhoven C, Haan J, Bakker E, Hardy JA, Van Hul W, Wehnert A, Vegter-Van der Vlis M, Roos RA. Amyloid beta protein precursor gene and hereditary cerebral hemorrhage with amyloidosis (Dutch). Science. 1990 Jun 1;248(4959):1120-2.

50. Hendriks L, van Duijn CM, Cras P, Cruts M, Van Hul W, van Harskamp F, Warren A, McInnis MG, Antonarakis SE, Martin JJ. Presenile dementia and cerebral haemorrhage linked to a mutation at codon 692 of the beta-amyloid precursor protein gene. Nat Genet. 1992 Jun;1(3):218-21.

51. Yagi-Utsumi M, Dobson CM. Conformational Effects of the A21G Flemish Mutation on the Aggregation of Amyloid β Peptide. Biol Pharm Bull. 2015;38(10):1668-72

52. Greenberg SM, Shin Y, Grabowski TJ, Cooper GE, Rebeck GW, Iglesias S, Chapon F, Tournier-Lasserve E, Baron JC. Hemorrhagic stroke associated with the Iowa amyloid precursor protein mutation. Neurology. 2003 Mar 25;60(6):1020-2.

53. Rovelet-Lecrux A, Hannequin D, Raux G, et al.: APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. Nat Genet. 2006; 38(1): 24–6.

54. Cabrejo L, Guyant-Maréchal L, Laquerrière A, et al.: Phenotype associated with APP duplication in five families. Brain. 2006; 129(Pt 11): 2966–76

55. Sleegers K, Brouwers N, Gijselinck I, et al.: APP duplication is sufficient to cause early onset Alzheimer's dementia with cerebral amyloid angiopathy. Brain. 2006; 129(Pt 11): 2977–83

56. Buss L, Fisher E, Hardy J, Nizetic D, Groet J, Pulford L, Strydom A. Intracerebral haemorrhage in Down syndrome: protected or predisposed?. F1000Research. 2016;5.

57. Sobey CG, Judkins CP, Sundararajan V, Phan TG, Drummond GR, Srikanth VK. Risk of major cardiovascular events in people with Down syndrome. PloS one. 2015 Sep 30;10(9):e0137093.

58. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol. 2010 Mar;6(3):131-44.

59. Lu H, Zhu XC, Jiang T, Yu JT, Tan L. Body fluid biomarkers in Alzheimer's disease. Ann Transl Med. 2015 Apr;3(5):70

60. Lui JK, Laws SM, Li QX, Villemagne VL, Ames D, Brown B, Bush AI, De Ruyck K, Dromey J, Ellis KA, Faux NG, Foster J, Fowler C, Gupta V, Hudson P, Laughton K, Masters CL, Pertile K, Rembach A, Rimajova M, Rodrigues M, Rowe CC, Rumble R, Szoeke C, Taddei K, Taddei T, Trounson B, Ward V, Martins RN, AIBL Research Group. Plasma amyloid-beta as a biomarker in Alzheimer's disease: the AIBL study of aging. J Alzheimers Dis. 2010;20(4):1233-42.

61. Head E, Doran E, Nistor M, Hill M, Schmitt FA, Haier RJ, Lott IT. Plasma amyloid-beta as a function of age, level of intellectual disability, and presence of dementia in Down syndrome. J Alzheimers Dis.2011;23:399–409

62. Schupf N, Patel B, Silverman W, Zigman WB, Zhong N, Tycko B, Mehta PD, Mayeux R. Elevated plasma amyloid beta-peptide 1-42 and onset of dementia in adults with Down syndrome. Neurosci Lett. 2001;301:199–203.

63. Prasher VP, Sajith SG, Mehta P, Zigman WB, Schupf N. Plasma beta-amyloid and duration of Alzheimer's disease in adults with Down syndrome. Int J Geriatric Psychiatry. 2010;25:202–207.

64. Matsuoka Y, Andrews HF, Becker AG, Gray AJ, Mehta PD, Sano MC, Dalton AJ, Aisen PS. The relationship of plasma Abeta levels to dementia in aging individuals with Down syndrome. Alzheimer Dis Assoc Disord. 2009;23:315–318

65. Coppus AM, Schuur M, Vergeer J, Janssens AC, Oostra BA, Verbeek MM, van Duijn CM. Plasma β amyloid and the risk of Alzheimer's disease in Down syndrome. Neurobiol Aging. 2012 Sep;33(9):1988-94

66. Shin RW, Iwaki T, Kitamoto T, Tateishi J. Hydrated autoclave pretreatment enhances tau immunoreactivity in formalin-fixed normal and Alzheimer's disease brain tissues. Laboratory investigation; a journal of technical methods and pathology. 1991 May;64(5):693-702.

67. Zetterberg H, Wilson D, Andreasson U, Minthon L, Blennow K, Randall J, Hansson O. Plasma tau levels in Alzheimer's disease. Alzheimers Res Ther. 2013 Mar 28;5(2):9

68. Mattsson N, Zetterberg H, Janelidze S, Insel PS, Andreasson U, Stomrud E, Palmqvist S, Baker D, Tan Hehir CA, Jeromin A, Hanlon D, Song L, Shaw LM, Trojanowski JQ, Weiner MW, Hansson O, Blennow K; ADNI Investigators. Plasma tau in Alzheimer disease. Neurology. 2016 Oct 25;87(17):1827-1835

69. Lee NC, Yang SY, Chieh JJ, Huang PT, Chang LM, Chiu YN, Huang AC, Chien YH, Hwu WL, Chiu MJ. Blood Beta-Amyloid and Tau in Down Syndrome: A Comparison with Alzheimer's Disease. Front Aging Neurosci. 2017 Jan 17;8:316.

70. Huang WJ, Zhang X, Chen WW. Role of oxidative stress in Alzheimer's disease. Biomed Rep. 2016 May;4(5):519-522

71. Strydom A, Dickinson MJ, Shende S, Pratico D, Walker Z. Oxidative stress and cognitive ability in adults with Down syndrome. Prog Neuropsychopharmacol Biol Psychiatry. 2009 Feb 1;33(1):76-80.

72. Garlet TR, Parisotto EB, de Medeiros Gda S, Pereira LC, Moreira EA, Dalmarco EM, Dalmarco JB, Wilhelm Filho D. Systemic oxidative stress in children and teenagers with Down syndrome. Life Sci. 2013 Oct 11;93(16):558-63.

73. Perluigi M, Butterfield DA. Oxidative Stress and Down Syndrome: A Route toward Alzheimer-Like Dementia. Curr Gerontol Geriatr Res. 2012;2012:724904.

74. Strydom A, Dickinson MJ, Shende S, Pratico D, Walker Z. Oxidative stress and cognitive ability in adults with Down syndrome. Prog Neuropsychopharmacol Biol Psychiatry. 2009 Feb 1;33(1):76-80.

75. Zis P, Dickinson M, Shende S, Walker Z, Strydom A. Oxidative stress and memory decline in adults with Down syndrome: longitudinal study. J Alzheimers Dis. 2012;31(2):277-83.

76. Armstrong RA, Cattell RJ, Jones SA, Winsper S, Blair JA. Elevated urinary neopterin suggests immune activation in Alzheimer's disease and Down's syndrome. Neuroscience Research Communications. 1994;14(2):63-69.

77. Parker DC, Mielke MM, Yu Q, Rosenberg PB, Jain A, Lyketsos CG, Fedarko NS, Oh ES. Plasma neopterin level as a marker of peripheral immune activation in amnestic mild cognitive impairment and Alzheimer's disease. Int J Geriatr Psychiatry. 2013 Feb;28(2):149-54.

78. Savas S, Kabaroglu C, Alpman A, Sarac F, Yalcin MA, Parıldar Z, Ozkinay F, Kumral E, Akcicek F. No relationship between lipoprotein-associated phospholipase A2, proinflammatory cytokines, and neopterin in Alzheimer's disease. Exp Gerontol. 2016 May;77:1-6.

79. Mehta PD, Capone G, Jewell A, Freedland RL. Increased amyloid beta protein levels in children and adolescents with Down syndrome. J Neurol Sci. 2007 Mar 15;254(1-2):22-7.

80. Coppus AW, Fekkes D, Verhoeven WM, Tuinier S, Egger JI, van Duijn CM. Plasma amino acids and neopterin in healthy persons with Down's syndrome. J Neural Transm (Vienna). 2007;114(8):1041-5.

81. Youn YC, Park KW, Han SH, Kim S. Urine neural thread protein measurements in Alzheimer disease. J Am Med Dir Assoc. 2011 Jun;12(5):372-6.

82. Munzar M, Levy S, Rush R, Averback P. Clinical study of a urinary competitve ELISA for neural thread protein in Alzheimer disease. Neurol Clin Neurophysiol. 2002;2002(1):2-8.

83. Praticò D. F(2)-isoprostanes: sensitive and specific non-invasive indices of lipid peroxidation in vivo. Atherosclerosis. 1999 Nov 1;147(1):1-10.

84. Praticò D, Clark CM, Lee VM, Trojanowski JQ, Rokach J, FitzGerald GA. Increased 8,12-iso-iPF2alpha-VI in Alzheimer's disease: correlation of a noninvasive index of lipid peroxidation with disease severity. Ann Neurol. 2000 Nov;48(5):809-12.

85. Praticò D. The neurobiology of isoprostanes and Alzheimer's disease. Biochim Biophys Acta. 2010 Aug;1801(8):930-3

86. Zis P, McHugh P, McQuillin A, Praticò D, Dickinson M, Shende S, Walker Z, Strydom A. Memory decline in Down syndrome and its relationship to iPF2alpha, a urinary marker of oxidative stress. PLoS One. 2014 Jun 5;9(6):e97709

87. Zis P, Strydom A, Buckley D, Adekitan D, McHugh PC. Cognitive ability in Down syndrome and its relationship to urinary neopterin, a marker of activated cellular immunity. Neurosci Lett. 2017 Jan 1;636:254-257.

88. Anoop A, Singh PK, Jacob RS, Maji SK. CSF biomarkers for Alzheimer's disease diagnosis. Int J Alzheimer Dis. 2010; 2010: 606802.#

89. Dekker AD, Fortea J, Blesa R, De Deyn PP. Cerebrospinal fluid biomarkers for Alzheimer's disease in Down syndrome. Alzheimers Dement (Amst). 2017 Mar 20;8:1-10

90. Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, Hölttä M, Rosén C, Olsson C, Strobel G, Wu E, Dakin K, Petzold M, Blennow K, Zetterberg H. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 2016 Jun;15(7):673-684

91. Tapiola T., Soininen H., Pirttilä T. CSF tau and Abeta42 levels in patients with Down's syndrome. Neurology. 2001;56:979–98

92. Portelius E., Hölttä M., Soininen H., Bjerke M., Zetterberg H., Westerlund A. Altered cerebrospinal fluid levels of amyloid β and amyloid precursor-like protein 1 peptides in Down's syndrome. Neuromolecular Med. 2014;16:510–516

93. Sogorb-Esteve A, García-Ayllón MS, Fortea J, Sánchez-Valle R, Lleó A, Molinuevo JL, Sáez-Valero J. Cerebrospinal fluid Presenilin-1 increases at asymptomatic stage in genetically determined Alzheimer's disease. Mol Neurodegener. 2016 Sep 29;11(1):66.

94. Praticò D, Clark CM, Liun F, Rokach J, Lee VY, Trojanowski JQ. Increase of brain oxidative stress in mild cognitive impairment: a possible predictor of Alzheimer disease. Arch Neurol. 2002 Jun;59(6):972-6.

95. Cossec JC, Lavaur J, Berman DE, Rivals I, Hoischen A, Stora S, Ripoll C, Mircher C, Grattau Y, OlivoMarin JC, de Chaumont F. Trisomy for synaptojanin1 in Down syndrome is functionally linked to the enlargement of early endosomes. Human molecular genetics. 2012 Apr 17;21(14):3156-72

96. Corlier F, Rivals I, Lagarde J, Hamelin L, Corne H, Dauphinot L, Ando K, Cossec JC, Fontaine G, Dorothée G, Malaplate-Armand C et al. Modifications of the endosomal compartment in peripheral blood mononuclear cells and fibroblasts from Alzheimer's disease patients. Translational psychiatry. 2015 Jul 1;5(7):e595.

Table 1: Comparison of Alzheimer's disease clinical phenotypes between Down syndrome, Duplication APP, and APP mutation types.

	Biological effect	**Memory/ cognitive decline**	**Behavioural/ emotional/ personality changes**	**Myoclonus/ seizures**	**Intra-cerebral haemorrhage/ stroke**
AD-type APP mutations e.g. Swedish mutation – KM670/671NL	Increased total Aβ Unchanged Aβ42/40	Prominent	Uncertain/rare	Late stages	Absent/Rare
London Mutation - V717I	Increased total Aβ42 Increased Aβ42/40 ratio	Prominent	Relatively prominent	Prominent	Absent/Rare

CAA-type APP mutations e.g. Dutch mutation E693Q; Italian mutation E693K	Altered APP processing, increased Aβ aggregation Reduced Aβ42/40 ratio	Late stages	Absent / Rare	Uncertain	Prominent
Duplication APP CNVs	APP overproduction, Aβ Subspecies ratios unknown	Prominent	Uncertain/ rare	Prominent	Prominent
Down syndrome	APP overproduction, Aβ Subspecies ratio unknown	Prominent	Prominent	Prominent	Occasional stroke

Table 2. Overview of peripheral and central biomarkers of Alzheimer's disease in Down syndrome. cnDS – cognitively normal Down syndrome subjects; dDS - Down syndrome subjects with clinically diagnosed Alzheimer's disease; SOD, superoxide dismutase; GPx, glutathione peroxidase; DS, down syndrome; AD, Alzheimer's disease, CSF, cerebrospinal fluid.

	Type of fluid	Biomarker	Importance
Peripheral	Blood	Amyloid-beta	DS vs. normal controls Higher Aβ42 and Aβ40 levels in subjects with DS [63] dDS vs. cnDS dDS subjects show increased Aβ42/Aβ40 ratio and increased Aβ40 levels [64, 65]
		Tau	DS vs. normal controls Higher plasma tau in DS dDS vs. cnDS Tau decreases in dDS, possibly due to burnout phenomenon during long-term neurodegeneration [69]
		Oxidative stress markers - SOD1/GPx - SOD levels - Neopterin	DS vs. controls Exacerbated oxidative stress in DS, which increases with age [72, 73]. dDS vs. cnDS Increased oxidative stress is associated with cognitive decline over time [75].

	Urine	Oxidative stress markers - Isoprostane 8,12-iso-iPF2alpha - Neopterin	DS vs. controls Subjects with DS show exacerbated oxidative stress [86, 87]. dDS vs. cnDS Increased oxidative stress is associated with cognitive decline over time [86].
Central	CSF	Amyloid-beta	DS vs. normal controls Lower CSF Aβ42 levels in DS subjects, and decrease with age. dDS vs. cnDS Whether CSF Aβ42 levels correlate with cognitive decline or dementia remains to be confirmed.
		Tau	DS vs. normal controls CSF tau levels increase with age in DS subjects. dDS vs. cnDS Whether tau levels correlate with cognitive decline or dementia remains to be confirmed.
		Presenilin-1	DS vs. normal controls CSF presenilin-1 is increased in DS subjects. dDS vs. cnDS Whether CSF presenilin-1 levels correlate with cognitive decline or dementia remains to be confirmed.
		Oxidative stress markers - Isoprostane 8,12-iso-iPF2alpha	No studies have included DS subjects yet. In normal controls, increased brain oxidative damage precedes the onset of symptomatic dementia; may help to identify a subgroup of patients with MCI with increased lipid peroxidation at increased risk to progress to symptomatic AD [94].

Highlights:

- Alzheimer's disease (AD) in Down syndrome (DS) presents with memory and cognitive decline, behavioural symptoms, myoclonus/seizures
- In comparison with Familial AD due to duplication APP, vascular complications such as stroke is rare
- More CSF biomarker studies are needed to explore differences in biological effects of APP mutations, duplication APP, and DS